Novel 1,4-Diphosphanes with Imidazolidin-2-one Backbones as Chiral Ligands: Highly Enantioselective Rh-Catalyzed Hydrogenation of Enamides**

Sang-gi Lee,* Yong Jian Zhang, Choong Eui Song, Jae Kyun Lee, and Jung Hoon Choi

Transition metal catalyzed asymmetric hydrogenation is one of the most powerful methods for the synthesis of optically active compounds, and the development of new chiral phosphanes plays a crucial role in this area.[1, 2] Since Kagan and Dang developed the first C_2-symmetric 1,4-diphosphane ligand (diop) in the early 1970s,[3] many diop analogues (**A** and **B** in Figure 1) have been synthesized and

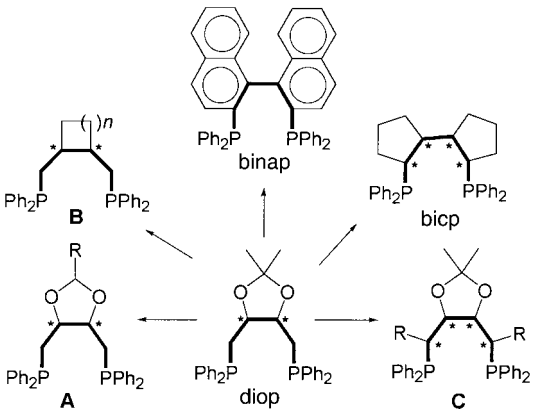


Figure 1. Various types of 1,4-diphosphanes forming seven-membered metal chelate rings.

applied in various asymmetric catalytic reactions.[4] However, the enantioselectivities obtained with these diop-type 1,4-diphosphane ligands are not always sufficiently high. It is generally believed that the low enantioselectivities with diop-type 1,4-diphosphanes are largely due to the formation of comformationally flexible seven-membered metal-chelate rings. Thus, transfer of backbone chirality through a methylene group to the phenyl group on the phosphane may not be efficient.[5] Only a few diphosphane ligands forming seven-membered metal chelates (e.g., axially chiral binap[6] and bicp[7]) achieved high enantioselectivities. More recently, ligands **C** have been introduced in which the configurations of the stereogenic centers are crucial to obtain high enantioselectivity.[8] Here we report a new type of 1,4-diphosphane ligands with an imidazolidin-2-one backbone, namely, (4*S*,5*S*)-4,5-bis(diphenylphosphanylmethyl)imidazolidin-2-ones **1** (bdpmi, Figure 2), which showed excellent enantioselectivities in Rh-catalyzed hydrogenation of α-arylenamides, a reaction that has attracted considerable attention recently.[9]

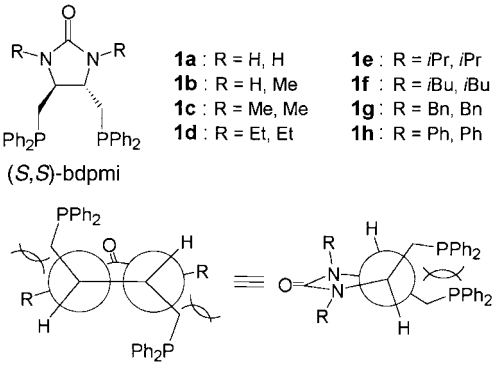
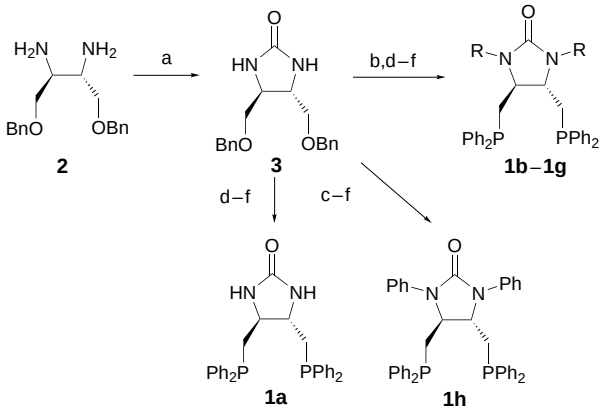


Figure 2. (*S*,*S*)-bdpmi ligands **1** and the Newman projection showing possible *gauche* interactions.

The design of the bdpmi ligands **1** was based on the following hypothesis: the consecutive *gauche* steric interactions between the N-substituents and phosphanylmethyl groups, as revealed in Newman projections (Figure 2), may influence the conformational flexibility of the seven-membered metal-chelate ring, and the enantioselectivity could therefore be strongly dependent on the steric nature of the R groups.

To test this hypothesis, a number of substituents R with different bulkiness were introduced on the nitrogen atom of imidazolidin-2-one (Scheme 1). Straightforward conversion of L-tartaric acid to the C_2-symmetric vicinal diamine **2**[10] and subsequent reaction of **2** with carbonyldiimidazole (CDI) led to the key intermediate **3** in 40% overall yield. Deprotection



Scheme 1. a) CDI (1.2 equiv), CH_2Cl_2, reflux, 4 h, 94%; b) NaH, RBr, THF, reflux; R = H, Me: 35%; Me, Me: 89%; Et, Et: 91%; *i*Pr, *i*Pr: 16%; *i*Bu, *i*Bu: 43%; Bn, Bn: 90%; c) PhBr, *t*BuONa, Pd-dppf, toluene, 96%; d) H_2/Pd–C, MeOH, RT, 82–99% or for R = Bn, $Pd(OH)_2$/C, cyclohexene, MeOH/EtOAc (1:1), reflux, 81%; e) TsCl (2.2 equiv), pyridine, 71–86% or for R = Bn: MsCl (2.2 equiv), Et_3N, CH_2Cl_2, 74%; f) $KPPh_2$, CH_2Cl_2, RT, R = H, H: 76%; H, Me: 73%; Me, Me: 70%; Et, Et: 67%; *i*Pr, *i*Pr: 74%; *i*Bu, *i*Bu: 77%; Bn, Bn: 74%; Ph, Ph: 70%. dppf = 1,1'-bis(diphenylphosphino)ferrocene.

[*] Dr. S.-g. Lee, Dr. C. E. Song, J. K. Lee
Life Sciences Division
Korea Institute of Science and Technology
P.O. Box 131, Cheongryang, Seoul 130-650 (Korea)
Fax: (+82) 2-958-5189
E-mail: sanggi@kist.re.kr
Y. J. Zhang, Prof. J. H. Choi
Department of Chemistry
Hanyang University
Seoul 133-791 (Korea)

[**] This work was supported by the Ministry of Science and Technology (National Research Laboratory Program).

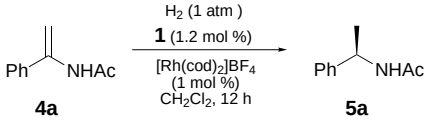
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/02/4105-0847 $ 17.50+.50/0

of the *O*-benzyl groups (after N-alkylation for **1b**–**1g**) and tosylation (mesylation for **1g**) followed by reaction with potassium diphenylphosphide afforded ligands **1a**–**1g**. The *N*-phenyl group of **1h** was introduced by using the Hartwig–Buchwald arylamination method.[11]

N-Acetylphenylethenamine (**4a**) was used as model substrate for hydrogenation. All reactions were carried out at 20 °C under 1 atm of H_2 and with an Rh:ligand ratio of 1:1.2 (Table 1).[12] Although a standard reaction time of 12 h was

Table 1. Rh-catalyzed asymmetric hydrogenation of *N*-acetyl phenylethenamine **4a** with **1a**–**1h** as chiral ligands.[a]



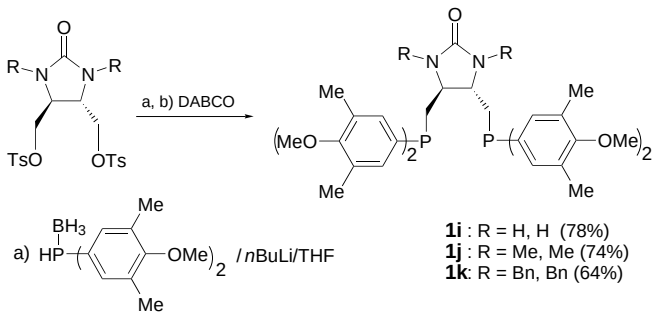
4a **5a**

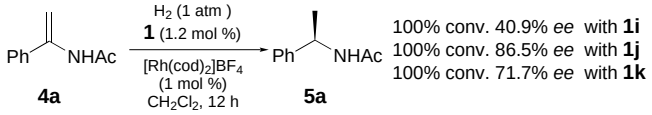
Entry	Ligand	Conv. [%][b]	*ee* [%][c]	Config.[d]
1	(*S*,*S*)-diop	100	60.2	*R*
2	**1a**	100	86.4	*R*
3	**1b**	100	94.0	*R*
4	**1c**	100	98.5	*R*
5	**1d**	100	97.3	*R*
6	**1e**	100	95.7	*R*
7	**1f**	100	97.2	*R*
8	**1g**	100	96.2	*R*
9	**1h**	100	94.6	*R*

[a] The reaction conditions were $[Rh(cod)_2]BF_4$:ligand:substrate 0.01:0.012:1, H_2 pressure 1 atm, reaction time 12 h, solvent CH_2Cl_2, room temperature. [b] Determined by ^1H NMR and GC analysis. [c] Determined by chiral GC on a CP-Chirasil-Dex CB column. [d] Determined by comparing the sign of the optical rotation with that reported in ref. [9b].

chosen, most reactions were complete within 4 h. With **1a**, which does not have N-substitutents, **4a** was hydrogenated to **5a** with 86.4% *ee* (entry 2). Under the same conditions, 60.2% *ee* was obtained with diop (entry 1). Introducing one *N*-methyl group (**1b**) increased the enantioselectivity to 94.0% *ee* (entry 3). The enantioselectivity was further increased with *N*,*N*-dimethylated ligand **1c** to 98.5% *ee* (entry 4). Comparison of the sense of asymmetric induction imparted by diop, **1a**, **1b**,and **1c** suggested that the steric interactions between the N-substituents and the phosphanylmethyl group is one of the key elements that controls enantioselectivity. However, N-substituents larger than methyl resulted in slightly lower enantioselectivities (entries 5–9), that is the *ee* values decreased with increasing *A* values of the N-substituents.[13]

Significantly lower *ee* values were obtained with **1i**–**1k**, synthesized by reaction of the tosylated intermediates for ligands **1a** and **1c** (mesylated for **1g**) with lithium bis(3,5-dimethyl-4-methoxyphenyl)phosphide–borane complex.[14] The NH ligand **1i** hydrogenated **4a** with only 40.9% *ee*, whereas the enantioselectivity with the *N*,*N*′-dimethylated ligand **1j** increased to 86.5% *ee* (Scheme 2). The ligands **1i**–**1k** possessing electron richer and bulkier phosphane groups uniformly give lower *ee* values than the corresponding **1a**, **1c**, and **1g**, and this indicates that steric effects alone may not be responsible for controlling enantioselectivity. However, the reason for the striking deterioration in enantioselectivity with **1i**–**1k** is not clear at present.



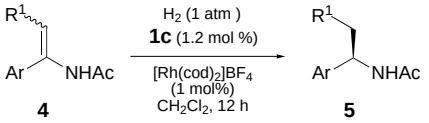


4a **5a**

Scheme 2. Synthesis of ligands **1i**–**k** and Rh-catalyzed hydrogenation of enamide **4a** with **1i**–**1k** as ligands. DABCO = 1,4-diaza[2.2.2]bicyclooctane.

The catalytic hydrogenation can be applied successfully to a series of α-arylenamides **4b**–**4g** to give chiral amine derivatives **5b**–**5g** with Me_2bdpmi **1c** (Table 2). In all cases, the *N*,*N*-dimethylated ligand **1c** exhibited excellent enantioselectivity. The electronic nature of the *para* substituents in α-phenylenamides has an effect on the enantioselectivity. Enamides with electron-donating substituents (**4b** and **4e**, entries 1 and 4 in Table 2) give higher enantioselectivity than those with electron-withdrawing substituents (**4c** and **4d**, entries 2 and 3). Remarkably, the mixtures of *E*- and *Z*-enamides **4g**–**4k** (*E*/*Z* = 1:2.0–2.5) were also reduced with very high enantioselectivities (> 99.0% *ee*, entries 6–10). It is noteworthy that the *ee* values of 97.8–99.0% obtained with bdpmi ligand **1c** are higher than or comparable to those obtained with other families of efficient chiral diphosphane ligands.[8, 9]

Table 2. Rh-catalyzed asymmetric hydrogenation of various *N*-acetyl α-arylenamides with **1c** as chiral ligand.[a]



4 **5**

Entry	**4**	Ar, R^1	Conv. [%][b]	*ee* [%][c]	Config.[d]
1	**4b**	*p*-MeC_6H_4, H	100	98.6	*R*
2	**4c**	*p*-FC_6H_4, H	100	97.9	*R*
3	**4d**	*p*-ClC_6H_4, H	100	97.8	*R*
4	**4e**	*p*-$MeOC_6H_4$, H	100	99.0	*R*
5	**4f**	2-naphthyl, H	100	> 99.0[e]	*R*
6	**4g**	C_6H_5, Me	100	> 99.0	*R*
7	**4h**	C_6H_5, Et	100	> 99.0	*R*
8	**4i**	*p*-$MeOC_6H_4$, Me	100	> 99.0	*R*
9	**4j**	*p*-ClC_6H_4, Me	100	> 99.0	*R*
10	**4k**	*p*-MeC_6H_4, Me	100	99.0	*R*

[a] The reaction conditions were $[Rh(cod)_2]BF_4$:**1c**:substrate 0.01:0.012:1, H_2 pressure 1 atm, reaction time 12 h, solvent CH_2Cl_2, room temperature. [b] Determined by ^1H NMR and GC analysis. [c] Determined by chiral GC on a CP-Chirasil-Dex CB column. [d] Absolute configurations were ascertained by comparison of the sign of optical rotation with that reported in ref. [9b]. [e] Determined by HPLC on a Chiralcel OD column.

  1433-7851/02/4105-0848 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2002**, *41*, No. 5

In summary, we have developed a new family of 1,4-diphosphanes **1** with an imidazolidin-2-one backbone as chiral ligands and showed their utility in the hydrogenation of α-enamides. The modular construction of this ligand class allows for wide structural diversity. Studies of this kind and mechanistic investigations are underway.

Experimental Section

For details on the synthesis of **1a**–**1k** and their precursors, see Supporting Information.

General procedure for the asymmetric hydrogenation of enamide **4**: **1** (0.0074 mmol) was added to a solution of $[Rh(cod)_2]BF_4$ (2.5 mg, 0.0062 mmol; cod = 1,5-cyclooctadiene) in CH_2Cl_2 (2 mL). After the reaction mixture had been stirred at 20 °C for 20 min, enamide **4** (0.62 mmol) was added. The hydrogenation was performed at 20 °C under 1 atm of hydrogen for 12 h. The reaction mixture was passed through a short silica gel column to remove the catalyst. The enantiomeric excess and the reaction conversion were measured by chiral GC or HPLC without any further purification.

Received: October 17, 2001 [Z18078]

[1] a) H. Takaya, T. Ohta, R. Noyori in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, pp. 1–39; b) *Comprensive Asymmetric Catalysis*, *Vol. 1–III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.

[2] Selected recent papers: a) T. Ireland, G. Grossheimann, C. Wieser-Jeunesse, P. Knochel, *Angew. Chem.* **1999**, *111*, 3397–3400; *Angew. Chem. Int. Ed.* **1999**, *38*, 3212–3215; b) G. Franciò, F. Faraone, W. Leitner, *Angew. Chem.* **2000**, *112*, 1486–1489; *Angew. Chem. Int. Ed.* **2000**, *39*, 1428–1430; c) M. T. Reetz, G. Mehler, *Angew. Chem.* **2000**, *112*, 4047–4049; *Angew. Chem. Int. Ed.* **2000**, *39*, 3889–3890; d) C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan, *J. Am. Chem. Soc.* **2000**, *122*, 11513–11514; e) U. Berens, M. J. Burk, A. Gerlach, W. Hems, *Angew. Chem.* **2000**, *112*, 2057–2060; *Angew. Chem. Int. Ed.* **2000**, *39*, 1981–1894.

[3] a) T.-P. Dang, H. B. Kagan, *J. Chem. Soc. Chem. Commun.* **1971**, 481; b) H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433.

[4] a) J. Gawroński, K. Gawrońska, *Tartaric Acid and Malic Acid in Synthesis*, Wiley, New York, **1999**, p. 332, and references therein. Selected recent papers: b) W. Hu, C.-C. Chen, G. Xue, A. S. C. Chan, *Tetrahedron: Asymmetry* **1998**, *9*, 4183–4192; c) M. Hayashi, Y. Hashimoto, H. Takezaki, Y. Watanabe, K. Saigo, *Tetrahedron: Asymmetry* **1998**, *9*, 1863–1866; d) V. Tararov, R. Kadyrov, T. H. Riermeier, J. Holz, A. Börner, *Tetrahedron Lett.* **2000**, *41*, 2351–2355.

[5] In Rh-catalyzed asymmetric hydrogenation, the orientation of phenyl groups of chiral diphenylphosphane ligands dictates the enantioselectivity. See: a) W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106–112; b) J. M. Brown, P. L. Evans, *Tetrahedron* **1988**, *44*, 4905–4916; c) J. S. Giovannetti, C. M. Kelly, C. R. Landis, *J. Am. Chem. Soc.* **1993**, *115*, 4040–4057; d) H. Brunner, A. Winter, J. Breu, *J. Organomet. Chem.* **1998**, *553*, 285–306.

[6] A. Miyashita, A. Yashuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934.

[7] G. Zhu, P. Cao, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 1799–1800.

[8] a) W. Li, X. Zhang, *J. Org. Chem.* **2000**, *65*, 5871–5874; b) Y.-Y. Yan, T. V. RajanBabu, *Org. Lett.* **2000**, *2*, 4137–4140.

[9] Only a few ligands are effective for Rh-catalyzed asymmetric hydrogenation of enamides: a) ref. [8]; b) M. J. Burk, Y. M. Wang, J. R. Lee, *J. Am. Chem. Soc.* **1996**, *118*, 5142–5143; c) F.-Y. Zhang, C.-C. Pai, A. S. C. Chan, *J. Am. Chem. Soc.* **1998**, *120*, 5808–5809; d) G. Zhu, X. Zhang, *J. Org. Chem.* **1998**, *63*, 9590–9593; e) D. Xiao, Z. Zhang, X. Zhang, *Org. Lett.* **1999**, *1*, 1679–1681; f) I. D. Gridnev, M. Yasutake, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2001**, *123*, 5268–5276.

[10] Application of the C_2-symmetric diamine **2** in the preparation of chiral ligands: a) T. Oishi, M. Hirama, *Tetrahedron Lett.* **1992**, *33*, 639–642; b) S.-g. Lee, C. W. Lim, C. E. Song, I. O. Kim, *Tetrahedron: Asymmetry* **1997**, *8*, 2927–2932; c) S.-g. Lee, C. W. Lim, C. E. Song, I. O. Kim, *Tetrahedron: Asymmetry* **1997**, *8*, 4027–4031; d) S.-g. Lee, C. W. Lim, C. E. Song, K. W. Kim, C. H. Jun, *J. Org. Chem.* **1999**, *64*, 4445–4451.

[11] a) Review: J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; b) A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902; c) J. Yin, S. L Buchwald, *Org. Lett.* **2000**, *2*, 1101–1104.

[12] The enantioselectivity was slightly decreased at a lower reaction temperature (95.7% *ee* at 6 °C) or higher hydrogen pressure (95.2% *ee* at 40 psi) with ligand **1g**. Other solvents such as acetone (95.6% *ee*), THF (93.9% *ee*), and MeOH (94.2% *ee*) were also examined with **1g** as chiral ligand.

[13] M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 5th ed., Wiley, New York, **2001**, p. 174.

[14] a) T. Imamoto, S. Kikuchi, T. Miura, Y. Wada, *Org. Lett.* **2001**, *3*, 87–90; b) T. Morimoto, M. Chiba, K. Achiwa, *Tetrahedron Lett.* **1989**, *30*, 735–738.

Mimicking Metallophosphatases: Revealing a Role for an OH Group with No Libido**

Marcello Forconi and Nicholas H. Williams*

Typically, descriptions of enzyme catalysis use multiple simultaneous interactions between the substrate and the active site to explain the remarkable efficiency which is normally observed.[1] This poses the intriguing question—do the different interactions operate cooperatively? That is, can a catalytic interaction have a bigger impact when it acts in concert with other complementary interactions than when it is used alone. This is difficult to mimic with simple compounds; usually when multiple interactions are introduced into a model system, it is found that they act independently rather than simultaneously, and such models generally do not rival enzyme efficiency.[2] Here we report how catalysis of phosphate monoester hydrolysis by an intramolecular OH group becomes much more effective when combined with catalysis by a dinuclear metal ion complex.

We have incorporated phosphate monoesters **1a**–**c** into dinuclear Co^{III} complexes **2a**–**c**. We have previously studied this type of complex as a structural and functional model for dinuclear metallophosphatases.[3] We wanted to investigate the effect of combining intramolecular general acid catalysis with this highly reactive core, as X-ray crystallography has revealed that as well as the metal ions in the active sites of metallophosphatase such as protein phosphatase-1 (PP-1) and kidney bean purple acid phosphatase (KBPAP), potential

[*] Dr. N. H. Williams, M. Forconi
Chemistry Department
University of Sheffield
Sheffield S3 7HF (UK)
Fax: (+44) 114-2738673
E-mail: N.H.Williams@Sheffield.ac.uk

[**] We thank the Royal Society and Nuffield foundation for financial support, and the BBSRC for a studentship (M.F.).

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.